A REVIEW OF THE PATHOLOGY AND ETIOLOGICAL FACTORS IN RHEUMATIC DISEASES

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PART I.

THE word "rheumatism" was first employed by Ballonius, a Parisian physician (1538-1616), to describe acute polyarthritis. Since then many writers have tried to define and crystallize the disease processes that are included in this vague and collective concept. Boerhaave, (Paul 1938), in 1737 recognized that besides the joint system, the disease invades "sometimes the brain, lungs, and bowels" and in more recent times (1927) Pappenheimer and Von Glahn recognized that the pathology of rheumatic infection extended beyond a mere study of the Aschoff nodule; they pointed out as equally distinctive, a more diffuse reaction, whether it occurs in the valves, the endocardium, the aorta, or the smaller vasculature.

Efforts to link acute rheumatic fever with arterial disease have been made for many years, particularly in France and Germany. In 1934, Friedberg and Gross presented four cases that came to autopsy, in which widespread periarteritis nodosa was associated with rheumatic fever and rheumatic heart disease, the latter being confirmed by the presence of Aschoff bodies in the myocardium. These workers presented evidence for a relationship between the two diseases and pointed out that both conditions have been considered by some to be the expression of an allergic reaction in a person sensitized to more than one agent rather than the result of infection by any one specific organism. This allergic hypothesis had been given great impetus by the investigations of Klinge in 1933, who reported that he had been able to produce lesions resembling those of rheumatic carditis by repeated injections of horse serum into rabbits.

In 1942, as a result of observations on patients who developed lesions of periarteritis nodosa which proved fatal following severe serum sickness, Rich and Gregory in 1943 experimentally produced typical diffuse periarteritis nodosa in rabbits by sensitizing these animals to sterile horse serum. They concluded that periarteritis nodosa is one manifestation of the anaphylactic type of hypersensitivity. They also noted that some of these animals sensitized to foreign serum developed acute diffuse glomerulonephritis.

Further experimentation by these workers in 1943 resulted in their being able to produce, in rabbits subjected to experimental serum sickness, cardiac lesions, which in their opinion closely resembled those of rheumatic carditis. They also drew attention to the fact that "a wide variety of lesions (erythemas, urticaria, purpura, arthritis, transient pareses, myocarditis, valvulitis, pericarditis, focal swelling and degeneration of collagen tissue, eosinophilia, necrosis and inflammation of arteries)" were common both to rheumatic fever and to the anaphylactic reaction of human or experimental serum sickness. They also stressed the similarity between the pulmonary lesions of rheumatic fever, the so-called rheumatic pneumonitis, with those resulting from anaphylactic hypersensitivity.

More recently McKeown (1947) produced lesions in the cardiovascular system of rabbits sensitized to horse serum which she considers to have the fundamental characteristics of rheumatic fever. In addition to a mere description of the morphological changes observed, she was able to demonstrate the developmental processes in the lesions from their incipient stages until their terminal fibrosis by killing her animals at increasing intervals after the second serum injection. She noted that the arterial lesions, present in 88% of her experimental animals, resembled closely those of periarteritis nodosa although they did not proceed to aneurysmal dilatation. Similarly, she demonstrated small granulomatous nodules occurring in the interstitial tissues of the myocardium which bore a very close resemblance to the Aschoff nodule in rheumatic fever, although the author is careful to point out that in 1935 Aschoff had denied that any experimental lesion produced up to that time had succeeded in duplicating the morphological structure of the rheumatic nodule.

The studies of Klemperer, Pollack, and Baehr in 1941 and 1942, and of Banks in 1941, finally resulted in the demonstration of a common denominator amongst certain morbid processes which the former workers referred to as

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the "diffuse collagen diseases". In studying the pathology of acute disseminated lupus erythematosus, Klemperer *et al.* were struck by the widespread damage to connective tissue throughout the body. All the elements of the connective tissue—cells, fibres, and ground substance—showed evidences of changes which were of the nature of a fibrinoid degeneration. They pointed out that other diseases in which widespread injury of collagen tissue played an outstanding rôle were rheumatic fever and diffuse scleroderma, (Pollack 1940), although in the latter case a sclerosis rather than a degeneration is the main feature. However, these workers believe that fibrinoid degeneration and sclerosis are merely two phases of the same underlying condition, namely a disturbance of the colloidal collagen system.

Previously both Rossle, in 1933, in his studies on rheumatic tissue changes and Jaeger, in 1932, in his investigation of thromboangiitis obliterans, had suggested that fibrinoid degeneration was constantly associated with an allergic diathesis and in this conviction they linked together rheumatic fever, periarteritis nodosa and thrombo-angiitis obliterans. Klemperer *et al.* in 1942 do not support this view, and question the classification of rheumatic fever as an allergic disease on the basis of fibrinoid degeneration being one of its characteristics. This has been reiterated recently by Baehr and Pollack (1947) and by Klemperer (1948) who do not feel that fibrinoid degeneration of itself is sufficient to warrant the classification of all such lesions into one allergic group although such changes in connective tissue have been experimentally produced. (Rich and Gregory 1943; McKeown 1947; Fox 1943.)

Teilum in 1945 and 1946, in studying the pathology of disseminated lupus erythematosus, described the miliary epithelioid-cell granulomata of the serosa and focal fibrinoid necrotizing processes in the free connective tissues as morphological criteria of the disease. Diseases such as lupus erythematosus disseminatus, arteriolitis granulomatosa, and periarteritis nodosa are described by this author as "pararheumatic diseases" with a common pathogenesis but probably due to a variety of etiological agents.

In a report of four fatal cases with severe allergic symptoms in which asthma had been a predominant feature, Bergstrand in 1946 noted pathological changes in the vessels characteristic of periarteritis nodosa and rheumatic fever. He observed fibrinoid degeneration of connective tissue in the lungs and rheumatic granulomata which he describes as identical with Aschoff nodules or rheumatic myocarditis. This author regards rheumatic fever whether arthritic or cardiac in its manifestations, periarteritis nodosa, and transient lung infiltration with eosinophilia (Löffler), as manifestations of an antigen-antibody reaction localized to different organs, and therefore related syndromes.

The efforts to classify "fibrositis" or "muscular rheumatism" with the diffuse collagen diseases have been singularly difficult because of the nebulous meaning of the entire concept of myofibrositis. The clinical diagnosis has been made so frequently on the strength of the subjective symptomatology of the patient, that the exact meaning of the term is not clear.

Stockman in 1920 dissected out some nodules in people with clinical signs and symptoms of fibrositis and studied them histologically. He reported certain non-inflammatory changes and endarteritis in the subcutaneous and myofascial connective tissues, but these were slight and indefinite. Slocumb in 1936 described a low-grade inflammatory sero-fibrinous exudate with proliferation of fibroblasts and blood vessels in the tender muscle areas as well as local tissue thickenings and the formation of gross subcutaneous nodules. However this too has been accepted in part only in the absence of more specific and consistent tissue changes. The whole hypothesis of myofascial inflammation remains an open one.

The pathological changes in rheumatoid arthritis have been studied extensively, both specifically and with the object of connecting them with the findings in rheumatic fever. Bennett in 1943 studied 48 autopsied cases of rheumatoid arthritis and 101 autopsied cases of rheumatic fever. Each series showed the characteristic changes of the respective diseases and the author concluded that because of the marked differences in the changes observed in the two series, the pathogenesis of these lesions must be different. It must be pointed out however that the author did not make any differentiation between the stages to which his various cases of rheumatoid arthritis had progressed. How many of these patients were in an acute and early phase of the disease and

how many were old chronic, burnt-out cases is not mentioned.

Baggenstoss and Rosenberg in 1941 and 1943 studied the possible relationship between rheumatoid arthritis and rheumatic fever and arrived at different conclusions. These workers reported the findings of rheumatic heart disease in 53% of 30 patients suffering from rheumatoid arthritis who came to autopsy. They also noted a low-grade, non-specific glomerulonephritis in 19 of their cases similar to the lesion which Bell in 1936 described as "glomerulitis". They suggested that rheumatoid arthritis and rheumatic fever may be closely related conditions. Other workers, namely Andrus (1941), Bayles (1943), Young and Schwedel (1944), have reported similar findings from autopsy material. Andrus, however, only mentions thickening of the left ventricular muscle of some of the chordæ tendineæ and of one of the leaflets of the mitral valve, but does not mention a myocarditis or Aschoff nodules. Similarly in the series reported by Bayles, 6 of 23 cases had gross cardiac changes at autopsy characteristic of those found subsequent to rheumatic fever, but histologic examination, except for one questionable case, failed to reveal active myocarditis. In the series examined by Young and Schwedel, 38 cases of rheumatoid arthritis were reported, 25 of these revealed gross cardiac lesions considered to be rheumatic in origin but in one case only were Aschoff bodies noted in the myocardium, and myocardial lesions thought to be healed Aschoff bodies were found in only two cases.

In a clinical pathological discussion of rheumatoid arthritis, Flynn in 1946 pointed out that the primary lesion of this disease is an inflammation of the synovial membrane which becomes enormously thickened by œdema, hyperæmia, and inflammatory cell infiltration.

Steinberg in 1941, in studying the pathology of rheumatoid arthritis noted two opposing processes, both in connective tissue, resulting in the destruction of the articular cartilage. On the surface of the articular cartilage there is a proliferation of the synovial membrane and production of a layer of granulation tissue, while deep to the cartilage a similar process involving the connective tissue of the bone marrow occurs. This extends through the zone of provisional calcification and destroys the articular cartilage from below while the disease in the synovial membrane above destroys the surface elements.

Bennett, Zeller, and Bauer in 1940 studied the subcutaneous nodules in cases of rheumatoid arthritis and rheumatic fever. They demonstrated obvious differences between these lesions, pointing out that the rheumatoid nodule was mainly one of central necrosis and outer proliferative activity of the connective tissue while the prominent feature of the rheumatic lesions is exudative. They suggested that these differences could be of use in differential diagnosis.

Recognizing the diffuse, systemic nature of rheumatoid arthritis, Freund, Steiner, Leichtentritt and Price in 1942 re-examined all the pathological changes found in the disease. They noted characteristic pathological nodules in the perineurium of the peripheral nerves. These nodules showed a central zone of necrosis, an intermediate zone of proliferating mesenchymal cells and a peripheral ring-like zone of inflammation with lymphocytes and plasma cells. Similar nodules, along with hydropic degeneration, swelling and atrophy of the muscle fibres were subsequently demonstrated in the muscles by Steiner, Freund, Leichtentritt, and Mann in 1946. They claimed these lesions as being specific for rheumatoid arthritis and were seen in every one of 9 cases examined, being absent from 196 routine controls. This nodular polymyositis was found throughout a great many muscles examined at random and was shown to fit in pathologically with the other lesions of this disease seen in the synovia, subcutaneous nodules and peripheral nerve trunks (*vide supra*). These findings have since been confirmed by Gibson, Kersley, and Desmarais in 1945. In a similar study, de Forest, Bunting and Kenney in 1947 found focal cellular accumulations of the above type in 2 of 4 control cases of "non-specific infectious" arthritis. They were absent from all other controls.

Recently, Clawson, Noble and Lufkin (1947) studied a group of seven muscles from each of 450 autopsy cases* dying from various conditions. This series was studied to furnish controls for a further series of 44 cases of rheumatoid arthritis wherein biopsy specimens from

* Of the seven muscles examined (pectoral, sternocleidomastoid, deltoid, diaphragm, intercostal, psoas, and sacrospinalis), the psoas was examined in 432 cases and the sacrospinalis in 150 cases.

the deltoid muscle were studied by Wells and Wetherby. The muscles were examined for nodular myositis, and muscular atrophy and degeneration described by Steiner *et al.* (1946). Clawson and his co-workers found deltoid lesions which they claim to be similar to those described by Steiner, in 38.6% of the cases of rheumatoid arthritis studied. In the 450 controls, they observed 118 cases of nodular myositis, an incidence of 26.2% in one or more of the muscles studied, but a much smaller figure (4.2%) when the deltoid muscle alone was examined. Degenerative lesions were observed more commonly than nodular lesions in the 450 cases, but there was definite overlapping between the two.

There were 6 cases of acute rheumatic fever in the series, all of which showed nodular myositis in one or more of the seven muscles.

These workers concluded that nodular myositis or muscular degenerative lesions, although commonly found in rheumatoid arthritis and acute rheumatic fever, are also found, though less frequently, in an ordinary series of autopsies. They also noted lesions more frequently in the muscles of older patients who came to autopsy.

In summary, it cannot be said that the histopathological findings recorded in the literature offer proof for bringing these diseases together into a single group. Nevertheless such a grouping as proposed by Klemperer, Pollack and Baehr in 1942 under the term "diffuse collagen diseases" is being employed as a convenient descriptive term by investigators.

Ragan in 1946 includes under this heading, serum sickness, rheumatic fever, rheumatoid arthritis, lupus erythematosus disseminatus, periarteritis nodosa, and scleroderma.

More recently Duff (1948) has reviewed the pathological process in the "diffuse collagen diseases" noting that the most characteristic histological change reported in this group is a fibrinoid necrosis of fibrous connective tissue. He contends that the connective tissues cannot be considered as a system but only as a tissue that is widely distributed throughout the body. In support of this contention this author emphasized the entirely passive nature of connective tissue in the body structure. He maintains that fibrinoid degeneration, proliferative changes and inflammatory reactions are all part of the pathological process under discussion, and that it is the degree to which each of the three pathological components contribute to the process, together with the anatomical distribution of the lesions concerned, that permit the identification of the various diseases as distinct clinical and pathological entities. He points out too, that until such time as further proof of a similarity of pathogenesis is established for these conditions, their grouping together under the term of diffuse collagen disease must be regarded as a "purely morphological correlation".

Etiological theories.—As for any disease for which no specific etiologic agent has been uncovered, the theories propounded in an effort to explain the cause of rheumatic disease have been manifold. Most investigations into the possible factors initiating rheumatoid arthritis have been paralleled by similar and frequently coincidental researches into possible explanations for rheumatic fever. Because of this, the following discussion will deal largely with these two diseases.

In the light of more recent work linking hæmolytic streptococci to rheumatic fever and rheumatoid arthritis, it will suffice merely to touch on some of the older points of view.

1. Many different forms of metabolic dysfunction have been suggested by different investigators as playing a primary rôle in the causation of these diseases. Abnormal sulphur metabolism, as measured by the cystine content of finger nails, was considered to be of etiologic significance by Argy in 1935, although he did not classify his arthritides beyond "nontuberculous arthritis". In the same year Wheeldon suggested that a sulphur deficiency in the joint cartilage as a result of deficient ability of the intestinal tract to absorb this element, was important in the causation of some forms of arthritis. Woldenberg in 1935 treated a large group of patients suffering from atrophic as well as hypertrophic arthritis, with colloidal sulphur, and claimed excellent results. However Senturia in 1935 studied the 24 hour sulphur excretion and partition in 18 cases of atrophic, and 14 cases of hypertrophic arthritis as well as in 20 healthy controls, and he found no significant differences between them. Freyberg, Block and Fromer in 1940 made detailed studies of sulphur metabolism in 4 cases of rheumatoid arthritis, 2 of osteoarthritis, and 3 of ankylosing spondylitis and came to the conclusion that no evidence of sulphur deficiency existed in arthritic patients.

Plasma cholesterol studies have also been made. In 1935 Hartung and Bruger studied the plasma cholesterol in 33 cases of rheumatoid arthritis and 59 cases of osteoarthritis, using 33 apparently normal controls. They tried to correlate the plasma cholesterol findings with the sedimentation rate, but could find no absolute correlation between them. They did conclude however, that the total cholesterol content of the plasma tended to be decreased in rheumatoid arthritis and elevated in osteoarthritis. In a further study of 12 cases of rheumatoid arthritis and 18 cases of osteoarthritis, Granirer in 1946 studied the plasma cholesterol, sedimentation rate and urinary cholesterol excretion and found no relationship between them.

It has long been known that jaundice (Hench 1933, 1938, 1940) or pregnancy (Hench 1938) will ameliorate the clinical activity of rheumatoid arthritis. Because of the very high levels of total lipids, phospholipids and total and free cholesterol found in jaundice, Block, Buchanan and Freyberg in 1941 made a comparative study of the lipid partition of serum on patients with obstructive jaundice, on patients with rheumatoid arthritis and on normals. They concluded that the serum lipids in patients with arthritis are not below normal and that jaundice is therefore not beneficial to arthritic patients by reason of correcting a lipid deficiency.

In 1944, Bayles and Riddell studied the question of the lipæmia of pregnancy as a possible cause for the amelioration of symptoms in pregnant arthritics. They also concluded that with active rheumatoid arthritis, the total cholesterol and phospholipid plasma content is normal, as well as the calculated lipids and lipid ratios. They also showed that the lipæmia of pregnancy in patients with active rheumatoid arthritis was the same as that of normal pregnant subjects.

2. Many workers have considered that the endocrine glands might play some part in the etiology of rheumatoid arthritis and rheumatic fever. Most of these ideas developed as a result of the observation of different types of arthritides associated with known endocrine disorders or with the administration of endocrine preparations to laboratory animals. Selye *et al.* in 1944 were able to produce an arthritis in rats by the parenteral administration of massive doses of desoxycorticosterone acetate. The joint lesions could be more easily produced in adrenalectomized or thyroidectomized animals when they were exposed to cold. They also performed unilateral nephrectomy in a group of these rats and gave them sodium chloride solution instead of drinking water. The further administration of desoxycorticosterone acetate to these animals resulted in finding evidences at post mortem of nephrosclerosis, periarteritis nodosa and rheumatic nodules in the heart. In contrast Selye *et al.* point to a report by Curschmann who recorded an arthritis in a case of Addison's disease.

The thyroid gland has also been considered in connection with chronic arthritis. In 1943, Duncan (1932) reviewed much of the literature concerning arthritis both in hypo- and hyper-thyroidism. He believed that thyroid dysfunction could produce articular lesions in accord with the altered physiologic state. He felt that hyperthyroidism could produce joint changes which, if untreated by thyroid surgery, go on to atrophic polyarthritis with characteristic contractures. On the other hand, he felt that hypothyroidism produced degenerative, slowly progressive joint lesions that could be greatly improved by the administration of thyroid extract.

Hall and Monroe in 1933 studied 150 cases of atrophic arthritis and 150 cases of hypertrophic arthritis. They noted that the signs and symptoms of hypothyroidism occurred more frequently in the hypertrophic group. In the atrophic group the basal metabolic rates were below minus ten in 35.6% and below minus fifteen in 17.7% of 106 patients, while in the hypertrophic group 34.2% had a basal metabolic rate below minus fifteen. He concluded that thyroid deficiency was apparently a contributing etiologic factor in certain patients with chronic arthritis.

Peers in 1936 reported on 39 cases of atrophic arthritis and noted that 30 had a basal metabolic rate of minus four or less, 21 were below minus nine and 8 were below minus nineteen. However, he concluded by stating that the true arthritic is not a myxœdematous individual. Nevertheless, Pemberton and Scull in 1941 pointed out that as a group about 30% of all arthritics have a somewhat lowered basal metabolic rate.

The rôle of the parathyroids has also been examined. Oppel in 1929 claimed that in 42 cases of ankylosing spondylitis he noted that

28 had a hypercalcæmia while 14 had a normal calcium level which he puts at 9 to 12 mgm. %. He did not state the method used for calcium determination. Because of the above and the ankylosis that follows in this disease, he theorized that this disease was due to hyperparathyroidism. He then performed a partial parathyroidectomy on 55 patients although histological study of 33 of his surgical specimens failed to reveal parathyroid tissue in 10 of them. He noted a drop in blood calcium in most cases postoperatively and claimed that marked improvement in joint mobility was noted although he gave no proper statistics of his own.

Schkurov in 1935 claimed both subjective and objective late improvement following partial parathyroidectomy in 36 of 40 cases of ankylosing spondylitis and atrophic arthritis. Hartung and Greene in 1935, in a careful study of 50 cases of rheumatoid arthritis, estimated serum calcium levels in these and in hundreds of control cases by the Clark-Collip modification of the Kramer-Tisdall method. They found essentially the same levels in the rheumatoid arthritics as in the controls and concluded that there was no evidence from this study that hyperactivity of the parathyroid glands is a factor in the production of arthritis.

Ropes, Rossmeisl and Bauer in 1943, studied calcium and phosphorus metabolism in 9 patients with rheumatoid arthritis and 3 patients with degenerative joint disease. These patients were kept on a weighed and measured intake and output and in nitrogen equilibrium. Urines and stools were collected in three-day periods and calcium and phosphorus estimations were carried out. They found a grossly normal picture in all the patients studied but a detailed analysis showed a slightly increased calcium excretion in patients with rheumatoid arthritis and a slightly decreased calcium excretion in individuals with degenerative joint disease. They were unable to explain this by any of the factors known to influence calcium metabolism.

According to Selye in 1944, the pituitary is probably also involved in "endocrine arthritis" although he admits that its etiologic rôle is as yet somewhat obscure. As examples he points to the hypertrophic osteoarthritis of acromegaly and to the fact that hypopituitary dwarfism has been claimed to predispose to the development of arthritis.

Much has been written on menopausal arthritis, but most authors question the true nature of the arthritis involved. Hall in 1938 studied 71 women with so-called arthritis occurring after castration. He noted that 53 of these patients suffered from arthralgia rather than from true arthritis. There were only 18 cases of true arthritis (atrophic, hypertrophic or mixed). These patients were treated with œstrogenic substances and he noted that in some cases where true arthritis was present, there was some improvement. This author concluded that there was some evidence that removal of ovarian hormones may lead to joint disturbances that are controllable by replacement theory, but that these cases were mostly arthralgias and he considers unproved the existence of true menopausal arthritis.

The consensus of the authors of the Ninth Rheumatism Review (Hench *et al.* 1948) is that there is no conclusive evidence that endocrine imbalance plays a part in the production of rheumatoid arthritis.

3. A deficiency of one or more vitamins has been suggested as a cause of rheumatoid arthritis by many workers. Race in 1937 reported a deficiency of plasma vitamin A in patients with atrophic arthritis. Hall, Bayles and Soutter in 1940 studied the dark-adaptation curves as measured by the biophotometer, to detect vitamin A deficiency. They studied 79 cases of rheumatoid arthritis and reported a borderline to severe vitamin A deficiency in 65% of the group. Vitamin A therapy however, gave no evidence of clinical improvement in the arthritis.

Rinehart in 1935 was able to produce an arthropathy in guinea pigs by withholding vitamin C and he believed that these lesions were very like those of rheumatoid arthritis. He held the opinion that vitamin C might be a factor in the etiology of this disease. Jacques in 1940 noted low plasma ascorbic acid in 47 of 48 patients with rheumatoid arthritis, whom he studied but he reported that vitamin C therapy had no effect on the clinical progress of the disease. Freyberg in 1942 obtained no correlation between the severity of the arthritis and the vitamin C content of the blood in his study of over 100 cases.

Vitamin D has been used for the treatment of rheumatoid arthritis and since 1935 has become very popular. Dreyer and Reed in 1935 were among the first to employ this substance

therapeutically in large doses but these workers noted at the time that "it is doubtful if there is any justification for assuming that arthritis in any form is a vitamin D deficiency disease". No direct evidence has appeared to change this point of view.

Vitamin B deficiency has occasionally been noted in these diseases and is reported by Freyberg, but the opinion stated in the Ninth Rheumatism Review of the American Rheumatism Association is that such deficiencies should be considered as complications not causes of the disease. Nevertheless, recent studies by Colburn and Moore (1943) in a small group of children with rheumatic fever suggested that there is a relationship between poor diets and this disease, possibly an increase in susceptibility to infection.

4. Various circulatory disturbances have been considered in the etiology of atrophic arthritis. Naide, Sayen and Comroe in 1945 felt that patients with rheumatoid arthritis showed a high vascular tone with a tendency to peripheral vascular spasm. The cold, clammy hands of rheumatoid arthritics were thought to fit this pattern. Steinbrocker and Samuels in 1941 studied the arterial circulation by oscillometric methods, of the lower extremities in patients with atrophic and hypertrophic arthritis. They noted that 65.9% of the former and only 35.2% of the latter showed abnormalities, usually vasomotor in type, in these vessels. Other workers, namely Benatt and Taylor (1940), using contrast baths were unable to find any specific type of vascular pattern or reaction in patients with rheumatoid arthritis.

5. Trauma has been considered among the possible causes but is thought to be a precipitating factor rather than a specific cause. (Ryden 1943).

6. In more recent years, the development of psychosomatic medicine has lent added impetus to the idea that psychogenic influences play a significant part in the etiology of rheumatoid arthritis. Short and Bauer (1942) accept the thesis that psychogenesis may be a contributing factor in the progression of this disease but feel that some other fundamental agent must also be present. Savage in 1941 observed large numbers of arthritics during the German air offensive against London, and noted that there was evidently a large psychological element in the production of rheumatoid arthritis. Others have gone on to describe a personality type that appears so frequently amongst sufferers from this disease. Halliday in 1944 summed up the typical rheumatoid personality as a person who restricts herself from adequate emotional expression. These people develop a high sense of duty and service to others, which, according to Johnson *et al.* (1947), is a masochistic method of handling latent aggression and hostility built up as a result of conflict during the early œdipal period, and now accompanied with marked guilt feelings. These authors describe such women as having a marked masculine protest, rejecting their feminine rôle in life and identifying themselves with masculine aggressiveness in all spheres of activity, whether athletics, social, or sexual. These people tend to discharge their unconscious emotional tendencies through the voluntary muscles, thus increasing muscle spasm and tension and it is this latter mechanism which is thought by some to be capable of producing an arthritic attack (Weiss and English 1943).

Others (Patterson *et al.* 1943) have considered the possibility of emotional reactions producing changes in the peripheral circulation which might be of etiological significance (Steinbrocker and Samuels 1941).

7. The "pathologic colon", the result of improper food digestion as well as infection was considered by Gutmann in 1935 to be a causative factor in rheumatoid arthritis. This theory of intestinal toxicosis was further expanded by Wiltsie in 1940, who believed that secondary infections with streptococci in the gastro-intestinal tract were responsible for a toxicity that resulted in atrophic arthritis. This theory has not been adequately supported by evidence according to Hench *et al.* (1941) although Bassler (1942) still considers absorption of toxins from the gastro-intestinal tract to be one of the important factors in the etiology of rheumatoid arthritis.

8. The theory of focal infection, *i.e.*, a focus anywhere in the body resulting in a bacteræmia or a toxæmia with secondary joint involvement, has had so many proponents that a review of the literature is impractical for this paper. The common foci wherein different pathogens may lodge and which have been considered of importance in etiology of rheumatoid arthritis and rheumatic fever include the throat, tonsils, paranasal sinuses, teeth, gums,

gall bladder, vermiform appendix, genito-urinary tract and skin.

In 1944, Davidson summed up the evidence both for and against focal infection being of importance in rheumatoid arthritis. He noted that, in favour of this theory, throat and sinus infections frequently precede attacks of the disease, removal of the focus sometimes leads to dramatic recovery, the histo-pathological picture of infected tonsillar tissue, sinuses and root abscesses suggest the absorption of toxic products into the general circulation, and temporary bacteræmia frequently occurs after tonsillectomy or tooth extraction. Against this theory, he pointed to the fact that frequently no focus of infection can be found, that in most cases removal of a focus does not result in a dramatic cure, and that many people in otherwise good health have infections in the same situations and of equal severity as those suffering from rheumatoid arthritis. He concluded with the observation that there is no proof that rheumatoid arthritis is caused by focal infection alone.

9. Viruses have also had their supporters. In 1935 Schlesinger *et al.* claimed to have found elementary bodies in inflammatory exudates of pericardium and pleura in patients dying of very acute rheumatic fever. These workers prepared a suspension of these bodies in formol saline and claimed specific agglutination of these particles by the sera of patients suffering from, but successfully resisting an acute rheumatic infection.

Eagles *et al.* in 1937, repeated this work and included suspensions from rheumatoid joints as well as from rheumatic fever exudates. They reported their findings as consistent with those of Schlesinger *et al.* and they considered this as evidence of a possible virus etiology for rheumatic disease. At present, the virus theory has few remaining adherents.

10. The theory of a relationship between acute rheumatic fever and rheumatoid arthritis on the one hand, and infection with hæmolytic streptococcus on the other, has received increasing attention from investigators. The work has been conveniently classified by Perry (1947) into three main groups: (*a*) The isolation of streptococci from rheumatic lesions. (*b*) Epidemiological studies of acute rheumatism following streptococcic infections. (*c*) The demonstration of antibodies to the hæmolytic streptococci in the blood of patients with acute rheumatism.

A further group may now be added as a result of the work of Cavelti in 1947, *i.e.*, the production of cardiac lesions in experimental animals by means of autoantibodies to heart and connective tissue.

(*a*) In 1920, Richards reported on joint cultures from 54 cases of chronic arthritis and claimed to have recovered streptococcus viridans in 4 cases. In 1929, Cecil, Nicholls and Stainsby made blood cultures from 78 patients with chronic infectious (rheumatoid) arthritis and reported finding a streptococcus in 61.5% of these cases. In 1931, these same investigators reported recovering streptococci from the blood of 62.3% of rheumatoid patients and none in healthy controls. They also reported recovering streptococci from the joints of 67.3% of rheumatoid patients and none from non-rheumatoid joints. Rabbits inoculated with these streptococci were shown to develop what the authors called rheumatoid arthritis, and recovery of the same streptococci from the blood and joints of the arthritic rabbits was also claimed.

In 1932 Gray and Gowen reported studies which agreed with the blood culture findings of Cecil *et al.*; however in the same year Dawson, Olmstead and Boots were unable to confirm the above findings. Blair and Hallman in 1934 failed to obtain any significant organisms from synovial fluids of 55 cases of rheumatoid arthritis and 2 cases of Still's disease. Similarly with rheumatic fever, Cecil, Nichols and Stainsby reported a high percentage of blood cultures positive for streptococci.

In 1943, Angevine, Rothbard and Cecil published a report on a four year study of blood and tissue cultures from all cases of rheumatoid arthritis and rheumatic fever that were available to them. These studies were carried out under very strict precautions. They were unable to isolate consistently any organism of significance.

Other workers at various times from 1920 on have reported the isolation of streptococci and other organisms from rheumatic fever patients and people with rheumatoid arthritis, but these reports were never consistent nor properly confirmed. In 1933 Callon reported positive cultures of either streptococcus viridans, streptococcus anhæmolyticus or pleomorphic bacilli in 70% of patients with rheumatic fever.

In 1939 Green reported that in 9 cases of acute rheumatic endocarditis, hæmolytic streptococci were cultivated from valves with macroscopic lesions in 8 cases and streptococci viridans in one case. No hæmolytic streptococci could be cultivated from valves without macroscopic lesions in the same cases.

(*b*) Other reports have followed similar patterns. The epidemiologic studies of Coburn and Pauli in 1932, who studied the relationship of streptococcal sore throat to rheumatic fever gave strong support to the idea that the hæmolytic streptococcus was in some way associated with activity of the rheumatic process in susceptible individuals. During the recent war, a number of studies on rheumatic fever were carried out in military camps (Thompson and Glazebrook 1941; Boisvert *et al.* 1943; Watson *et al.* 1945; Rantz *et al.* 1945; Wright 1945) and most of these reports strongly indicated that any increase in the incidence of rheumatic fever was preceded by an increase in acute hæmolytic streptococcal infections. However no definite specific serological types have been incriminated.

(*c*) Antibody studies have been made by various investigators in an effort to link the group A hæmolytic streptococcus to rheumatic disease. At first relatively gross, non-specific serological reactions were studied. In 1913 Hastings, using a complement-fixation test, obtained positive complement-fixation with the serum of arthritic patients and strains of streptococci isolated from foci of infection.

In 1930, Cecil, Nicholls and Stainsby reported finding agglutinins for hæmolytic streptococcus in the serum of patients with rheumatoid arthritis and similar findings were reported by Dawson, Olmstead and Boots in 1932. Subsequently it was shown that hæmolytic streptococci produced a variety of antibodies, each specific for a particular fraction of the organism. Thus precipitins could be demonstrated against the group specific "C" substance of Lancefield (1928) and the "D", "E", and "K" protein fractions of Heidelberger and Kendall (1931).

Antistreptolysins "O" and "S" were demonstrated by Todd in 1932 and 1938 and in 1933 Tillet, Edwards and Garner demonstrated antifibrinolysins in the sera of patients convalescent from acute hæmolytic streptococcal infections.

Coburn and Pauli in 1935 and 1939 showed that the antistreptolysin titres rise and persist in patients with active rheumatic fever, whereas in uncomplicated streptococcal throat infections, they reach their maximum in three weeks and subside. Similarly anti-M precipitins which were known to occur in non-rheumatic subjects following hæmolytic streptococcal throat infections (Swift and Hodge 1936), were also shown by these workers to persist longer than normally in the rheumatic subjects.

Bunim and McEwen in 1940 found high antistreptolysin titres in about 70% of their patients with active rheumatic fever, but found normal titres in nearly all cases of rheumatoid arthritis uncomplicated by recent upper respiratory infection.

Cecil and de Gara in 1939, however, noted that the only really specific reaction described for rheumatoid arthritis up to 1946, was the streptococcal agglutination reaction. They found 60.4% of 268 patients with rheumatoid arthritis had agglutinins for hæmolytic streptococci in a serum dilution of at least 1:160. Only 1 of 95 patients with osteoarthritis showed similar agglutinins. No agglutinins were found in 8 cases of rheumatic fever and in 27 normal controls.

Todd, Coburn and Hill in 1941 described two types of streptococcal hæmolysin, "O" and "S". They pointed out that antistreptolysin "O" was higher after a streptococcal infection in rheumatic than in non-rheumatic children and higher still during the acute phase of rheumatic fever.

Mote and Jones in 1941 undertook a study of antistreptolysin "O", antifibrinolysin, and precipitins to the "C", "D", "E", "K" and "P" fractions of the hæmolytic streptococcus in a group of individuals convalescent from streptococcal infections. These data were then compared with similar information obtained from a group of rheumatic fever patients. They found no difference in the hæmolytic and rheumatic individuals in their reaction to infection by the hæmolytic streptococcus. They concluded that streptococcal infections were of importance in rheumatic fever, but the mechanism involved was not explained.

Taran, Jablon and Weyr in 1944 prepared a combined material from the type specific M protein of 25 different Griffith types of hæmolytic streptococcus. This was then used to test for

skin reactivity in a group of rheumatic children and a group of non-rheumatic controls. They found the incidence of positive cutaneous reactions in normal children to be 65% as compared with 83% in rheumatic children. The incidence of positive cutaneous reactions in the normal siblings of these rheumatic children was the same as in rheumatic children. This seems to point to an individual or familial susceptibility towards reaction to hæmolytic streptococcal infection. The idea of an inherited predisposition to rheumatic disease is not new, and recently Wilson (1947) pointed out that the distribution of rheumatic fever cases in families followed the general laws of recessive Mendelian inheritance.

(*d*) The recent work of Cavelti is of great interest. This author claims to be able to produce autoantibodies to kidney (1945) and to heart (1947) in rats and rabbits by injecting renal or cardiac material respectively in combination with group A hæmolytic streptococcal substances. He noted that as a result of the renal autoantibody reaction with the rat's kidney *in situ,* acute and chronic glomerulonephritis was produced. Similarly, by injecting cardiac and connective tissue material in combination with streptococcal substances, he obtained pathologic changes in the valves and other connective tissue structures of the hearts of many of his experimental animals which he attributed to a reaction occurring between the autoantibodies formed and the corresponding tissues *in vivo.* These changes are considered by this investigator to be analogous, in a broad sense, to those of rheumatic fever.

This work along with that of Rich and Gregory in 1943, Bergstrand in 1946, McKeown in 1947, and others is leading many investigators to believe that the etiology and pathogenesis of rheumatic fever and rheumatoid arthritis may be dependent upon some connective tissue hypersensitivity reaction to certain products of group A hæmolytic streptococcus.

Hyaluronic acid and hyaluronidases.—**In 1934,** Meyer and Palmer reported the isolation of a polysaccharide acid of high molecular weight from the vitreous humour of cattle eyes. The salts of this substance which they named "hyaluronic acid", formed highly viscous solutions. In 1936, these same investigators reported isolating hyaluronic acid from human umbilical cords and in 1937, Kendall, Heidelberger and Dawson identified hyaluronic acid as a capsular constituent of groups A and C hæmolytic streptococci. Two years later Meyer, Smyth and Dawson showed hyaluronic acid to be present in bovine and human synovial fluid. Meyer and Palmer were able to demonstrate in 1936 that hyaluronic acid consisted of equimolar concentrations of N-acetylglucosamine and glucuronic acid although its exact structure is still unknown. Meyer (1947) has recently suggested that the marked viscosity of the substance may be due to its high degree of polymerization. Since its discovery, it has been obtained from many sources and is known to occur in large quantities in skin and to be one of the mucopolysaccharide components of interfibrillar, connective tissue ground substance. (Combined Staff Clinics College of Physicians and Surgeons, Columbia University, 1946; Meyer 1947). Efforts have been made by Morrison in 1941 and by Humphrey in 1943 to confer antigenicity to hyaluronic acid, but this has not been successful up to the present time.

An enzyme, hyaluronidase, which hydrolyzed hyaluronic acid and yielded reducing substances from it, was first reported by Meyer, Dubos and Smyth in 1936. These workers obtained the enzyme from the autolysates of a rough type 2 pneumococcus. In 1940, Meyer *et al.* described a method of preparing hyaluronidase from pneumococcus as well as from a group A hæmolytic streptococcus and from *Cl. Welchii.* The enzyme prepared from these sources was able to hydrolyze and reduce the viscosity of hyaluronic acid but was shown not to be the essential enzyme in the bacteriolytic system of the pneumococcus.

In 1941, McLean showed that those streptococci which produced capsules did not produce hyaluronidase and that capsules and hyaluronidase could not coexist in the same organism, since the enzyme destroyed the capsular substance. McClean showed too, that the inclusion of hyaluronidase in the medium in which streptococci which normally develop capsules were to be grown, prevented the appearance of capsules on these organisms. These capsules had been shown to contain hyaluronic acid (*vide supra*).

In 1930 and 1931 McClean, working in England, and Hoffman and Duran-Reynals in 1931, working independently in America, obtained a

substance from mammalian testicle which was able immediately to increase the permeability of connective tissues. McClean was also able to obtain this effect with extracts of spermatozoa. Similar spreading factors were obtained from extracts of staphylococci and streptococci (Duran-Reynals 1933), from organisms of the gas gangrene group and from pneumococci (McClean 1936). In 1937, Claude obtained a spreading factor from leech extracts and in 1939, Duran-Reynals demonstrated the presence of spreading power in snake and spider venoms. A review of the entire subject was published by Duran-Reynals in 1942.

In 1940, Chain and Duthie, using viscosimetric methods, reported close agreement between the viscosity - reducing activity of hyaluronidase preparations from many sources and their spreading activity in rabbit skin. These investigators concluded that the spreading factors of Duran-Reynals and McClean were identical with the enzyme hyaluronidase. They found hyaluronidase in all sources of spreading factor and reported that no spreading effect was obtained in the absence of hyaluronidase. They suggested that the mechanism of increased skin permeability produced by spreading factors was in reality due to a reduction in the viscosity of the hyaluronic acid contained in the skin, by the hyaluronidase of the spreading factor injected.

In 1941 however, Hobby *et al.* reported slightly different findings on the relationship between spreading factor and hyaluronidase. They studied spreading effect by intracutaneous injections in albino rabbits and hyaluronidase activity by hydrolysis of hyaluronic acid with production of reducing substances and by viscosimetry. They found that all preparations containing hyaluronidase also contained spreading factor but that many substances which contained marked spreading properties, possessed no hyaluronidase activity. These workers were able to prepare antisera to hyaluronidase preparations which specifically and completely inhibited the hydrolysis activity of the homologous enzyme but did not inhibit the spreading factors in the same preparations. It was therefore believed that spreading activity and enzyme activity were not identical actions.

As noted by Kendall *et al.*, in 1937, only streptococci in the mucoid phase, *i.e.*, encapsulated organisms, contain hyaluronic acid. Seastone in 1943 examined 125 strains of group A hæmolytic streptococci obtained from various human infections and found that about 94% of these strains produced hyaluronic acid in greater or less amount. In a group of group A hæmolytic streptococci from normal throats, only about 8% produced this substance. On the basis of these findings, this investigator pointed out the possible significance of the mucoid polysaccharide (hyaluronic acid) in streptococcal virulence.

Hyaluronidase, on the other hand, has been obtained from relatively few group A hæmolytic streptococci and these were all non-capsulated. Hobby *et al.* in 1941, and McClean in 1941, were able to obtain the enzyme in group A hæmolytic strains only from type 4 streptococci. Crowley in 1944 examined 308 strains of group A streptococci for hyaluronidase production and only two serological types, 4 and 22, were positive for the enzyme. Nevertheless, Meyer in 1947 pointed out that hyaluronidase activity *in vitro* varied greatly with many factors and that the enzyme might therefore be inactivated under *in vitro* experimental conditions. On the other hand *in vivo* skin testing frequently gave pronounced spreading reaction, regardless of the *in vitro* titre of hyaluronidase activity. This apparent anomaly was explained by this author on the basis of probable reversibility of the inactivating process in *in vivo* experiments. Meyer questioned whether failure to demonstrate hyaluronidase in more strains was necessarily due to absence of the enzyme.

Morrison in 1941 speculated on the possible relationship between streptococcal hyaluronic acid and that found in synovial fluid. He suggested the possibility of the mononuclear cells in the body becoming sensitized to the whole streptococcus as a result of repeated infections. Considering the large amounts of hyaluronic acid in certain tissue elements, he pointed to the possibility that the specific polysaccharide in the connective tissue ground substance might then act as an allergen and be the basis for a localization of such lesions as are attributed to streptococcal allergy.

In view of the foregoing considerations, the evidence which suggests the possibility that rheumatic disease may depend upon some mechanism involving a connective tissue hypersensitivity reaction to hæmolytic streptococci or their products, perhaps through a hyaluronic acid-hyaluronidase system, can be summarized as follows: (1) One of the highest con-

centrations of hyaluronic acid in the mammalian body is to be found in synovial fluid (Meyer *et al.* 1948). (2) Hyaluronic acid is an important component of connective tissue ground substance. (3) Rheumatic diseases have been shown to be primarily connective tissue diseases. (4) Hyaluronic acid is produced by most group A and C hæmolytic streptococci and is produced by all encapsulated strains. (5) Certain non-encapsulated group A and C hæmolytic streptococci produce hyaluronidase. (6) Much evidence exists linking rheumatic fever and rheumatoid arthritis to streptococcal infection. (7) There is increasing evidence in favour of an allergic basis for rheumatic disease.

Recently Meyer and Ragan (1948) reported a difference between normal and pathologic synovial fluids. This difference was expressed by a factor obtained from the log. of the viscosity of the fluid divided by the concentration of the contained hyaluronic acid. The pathologic specimens were taken from cases of rheumatic fever and rheumatoid arthritis and it was noted that the mathematical factor obtained varied inversely with the activity of the disease.

A somewhat different approach to the problem has been reported from Mexico by Guerra (1946). This author noted that administration of salicylic acid reduced the activity of hyaluronidase as a spreading factor in albino rabbits, whereas sulfadiazine actually enhanced its action. In a further group of experiments this author gave intradermal injections of hyaluronidase to individuals with active rheumatic fever or to those who had suffered with this disease in the past. In these people an enormous effusion of the dye with local œdema was noted but here too, administration of salicylates lessened this reaction.

In 1947, Pike tried to demonstrate this inhibitory action of salicylic acid *in vitro*. This investigator incubated bull testis hyaluronidase with a mucoid strain of streptococci and watched the rate of disappearance of the capsules. The addition of salicylic acid to this medium had no effect on the rate of capsule disintegration. The same negative results were obtained with the use of the mucin clot prevention test.

Lowenthal and Gagnon in 1947 showed that it was not the salicylic acid that inhibited the hyaluronidase but probably one of the metabolic breakdown products of salicylic acid, such as gentisic acid (Kapp and Coburn 1942). They noted that the quinone of gentisic acid inhibited the viscosity reducing effect of hyaluronidase on its substrate *in vitro*. Meyer and Ragan in 1948 have since reported a number of water-soluble quinones and hydroquinones to be inhibitors of hyaluronidase.

Dorfman, Reimers and Ott in 1947, however, reported that in their experiments with bull testis and *Cl. perfringens* hyaluronidase, salicylic acid did show inhibitory activity *in vitro*. But these authors admit that the required concentration of sodium salicylate is considerably above that obtained therapeutically.

Antisera to hyaluronidase have been shown to occur naturally and have been prepared experimentally by a number of workers (Duran-Reynals 1932; McClean 1936; McClean and Hale 1941; McClean 1942). McClean in 1942 showed too, that these sera were specific according to the source of the enzyme used. Thus sera prepared against hyaluronidases from *Cl. Welchii* and *Vibrion septique* are species—but not type—specific. Similarly those sera obtained against streptococcal hyaluronidases are group—but not type—specific.

In 1947, Friou and Wenner reported their studies in which they looked for streptococcal hyaluronidase inhibitors in the sera of a group of patients with a history of recent (one year or less) rheumatic fever or who were convalescent from recent hæmolytic streptococcal infections. A group of 23 normal controls was also included in the study. These authors used a modification of the mucin clot prevention test described by McClean *et al.* in 1943. They found inhibitory substances in many of the sera tested. These sera were shown to neutralize the hyaluronidase which they obtained from a group A, type 4 hæmolytic streptococcus. The inhibitory substances appeared to be present in greater amounts in the sera of the rheumatic fever group and in those convalescent from recent streptococcal disease, than in the group of normal controls. However, some members in the control group showed comparatively high levels of hyaluronidase inhibition. It was further shown that inhibitory substances seemed to appear in increasing amounts with advancing age.

(*To be continued*)